Date of Approval: March 24, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION (ANADA)

ANADA 200-810

Enrofloxacin Flavored Tablets

(enrofloxacin)

Flavored Tablets

Dogs and cats

Enrofloxacin Flavored Tablets are indicated for the management of diseases associated with bacteria susceptible to enrofloxacin. Enrofloxacin Flavored Tablets are indicated for use in dogs and cats.

Sponsored by:

Hikma Pharmaceuticals USA, Inc.

Executive Summary

Enrofloxacin Flavored Tablets (enrofloxacin) are approved for the management of diseases associated with bacteria susceptible to enrofloxacin in dogs and cats. The reference listed new animal drug (RLNAD) is Baytril® (enrofloxacin)Taste Tabs®, sponsored by Elanco US Inc., under NADA 140-441.

Bioequivalence

The sponsor conducted one *in vivo* blood-level study in dogs to show that the 136 mg Enrofloxacin Flavored Tablets are bioequivalent to the 136 mg Baytril® Taste Tabs®. No serious adverse events were reported during the study. The sponsor also conducted one *in vivo* blood-level study in cats to show that the 22.7 mg Enrofloxacin Flavored Tablets are bioequivalent to the 22.7 mg Baytril® Taste Tabs®. No serious adverse events were reported during the study.

The sponsor conducted a comparative *in vitro* dissolution study for the additional product strengths. Based on the dissolution data, the 22.7 mg and 68 mg flavored tablet strengths for use in dogs and the 68 mg and 136 mg flavored tablet strengths for use in cats qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver). FDA granted a biowaiver for these strengths.

Conclusions

Based on the data submitted by the sponsor for the approval of Enrofloxacin Flavored Tablets, FDA determined that the drug is safe and effective when used according to the label.

Table of Contents

I. GENERAL INFORMATION

A. File Number

ANADA 200-810

B. Sponsor

Hikma Pharmaceuticals USA, Inc.
2 Esterbrook Lane
Cherry Hill, NJ 08003

Drug Labeler Code: 086194

C. Proprietary Name

Enrofloxacin Flavored Tablets

D. Drug Product Established Name

enrofloxacin

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Flavored tablets

G. Amount of Active Ingredient

22.7 mg, 68 mg, or 136 mg of enrofloxacin per tablet

H. How Supplied

22.7 mg strength in bottles containing 100 and 500 double scored tablets
68 mg strength in bottles containing 50 and 250 double scored tablets
136 mg strength in bottles containing 50 and 200 double scored tablets

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Dogs: Administer orally at a rate to provide 5 - 20 mg/kg (2.27 to 9.07 mg/lb) of body weight. Selection of a dose within the range should be based on clinical experience, the severity of disease, and susceptibility of the pathogen. Animals which receive doses in the upper-end of the dose range should be carefully monitored for clinical signs that may include inappetence, depression, and vomition.

Weight of Dog	**Once Daily Dosing Chart**			
	5.0 mg/kg	10.0 mg/kg	15.0 mg/kg	20.0 mg/kg
9.1 kg (20 lb)	2 x 22.7 mg tablets	1 x 22.7 mg plus 1 x 68 mg tablets	1 x 136 mg tablet	1 x 136 mg plus 2 x 22.7 mg tablets
27.2 kg (60 lb)	1 x 136 mg tablet	2 x 136 mg tablets	3 x 136 mg tablets	4 x 136 mg tablets

Cats: Administer orally at 5 mg/kg (2.27 mg/lb) of body weight. The dose for dogs and cats may be administered either as a single daily dose or divided into two (2) equal daily doses administered at twelve (12) hour intervals. The dose should be continued for at least 2 - 3 days beyond cessation of clinical signs, to a maximum of 30 days.

Weight of Cat	**Once Daily Dosing Chart (5 mg/kg/day)**
5 lb (2.27 kg)	1/2 x 22.7 mg tablet
10 lb (4.5 kg)	1 x 22.7 mg tablet
15 lb (6.8 kg)	1 and 1/2 x 22.7 mg tablets or 1/2 x 68 mg tablet

K. Route of Administration

Oral

L. Species/Class

Dogs and cats

M. Indication

Enrofloxacin Flavored Tablets are indicated for the management of diseases associated with bacteria susceptible to enrofloxacin. Enrofloxacin Flavored Tablets are indicated for use in dogs and cats.

N. Reference Listed New Animal Drug

Baytril® Taste Tabs®; enrofloxacin; NADA 140-441; Elanco US Inc.

II. BIOEQUIVALENCE

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, allows for an abbreviated new animal drug application (ANADA) to be submitted for a generic version of an approved new animal drug (RLNAD). The ANADA sponsor is required to show that the generic product is bioequivalent to the RLNAD, which has been shown to be safe and effective. Effectiveness, target animal safety and human food safety data (other than tissue residue data) are not required for approval of an ANADA. If bioequivalence is

demonstrated through a clinical endpoint study in a food-producing animal, then a tissue residue study to establish the withdrawal period for the generic product is also required.

For this ANADA, two *in vivo* blood-level studies were conducted to demonstrate product bioequivalence using the generic and RLNAD enrofloxacin 136 mg flavored tablets in dogs and 22.7 mg flavored tablets in cats. The RLNAD is available in 22.7 mg, 68.0 mg, and 136.0 mg flavored tablet sizes. The *in vivo* blood-level study was conducted in 30 healthy, fasted dogs, and the *in vivo* blood-level study in cats was conducted in 30 healthy, fasted cats. The pivotal parameters to evaluate bioequivalence are the observed maximum plasma drug concentration (C_{MAX}) and area under the concentration-time curve (AUC) from time 0 to the last sampling time before the first unquantifiable concentration after C_{MAX}. Bioequivalence was demonstrated between the 136 mg RLNAD enrofloxacin flavored tablets and the 136 mg generic enrofloxacin flavored tablets in dogs, and the 22.7 mg RLNAD enrofloxacin flavored tablets and the 22.7 generic enrofloxacin flavored tablets in cats by the average bioequivalence approach as described in the Statistical Methods section below. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 22.7 mg and 68 mg flavored tablets in dogs and for the generic 68 mg and 136 mg flavored tablets in cats was requested. Dissolution data was used to demonstrate that the generic 22.7 mg and 68 mg flavored tablets are comparable to the generic 136 mg flavored tablet strength used in the *in vivo* blood-level bioequivalence dog study and the generic 68 mg and 136 mg flavored tablets are comparable to the generic 22.7 mg flavored tablet strength used in the *in vivo* blood-level bioequivalence cat study. Therefore, a biowaiver for the generic 22.7 mg and 68 mg generic flavored tablets in dogs and the generic 68 mg and 136 mg flavored tablets in cats was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: Pivotal Bioequivalence Study of Baytril® (Enrofloxacin) Taste Tabs® and Generic Enrofloxacin Flavored Tablets Administered Orally to Beagle Dogs under Fasted Conditions. (Study No. AKR501-003)

Study Dates: March 3, 2022 to July 26, 2022

Study Locations:

In-life phase: Ontario, Canada

Bioanalytical testing: Somerset, New Jersey

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 136 mg Enrofloxacin Flavored Tablets and the RLNAD 136 mg Baytril® (enrofloxacin) Taste Tabs® in fasted dogs.

Study Animals: Thirty intact male Beagle dogs between 414 to 1075 days of age on study day 0 and weighing 9.1 to 12.0 kg (when weight was measured in acclimation on study day -3).

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies.

Drug Administration: Each animal received 136 mg of either the generic or RLNAD enrofloxacin according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The plasma concentrations of enrofloxacin were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health and adverse events.

Statistical Methods:

The laboratory study was conducted as a randomized, masked two-period, two-sequence, two-treatment, single-dose crossover design using 30 dogs with a 7-day washout between periods. Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C_{MAX} and AUC. Time to maximum concentration (T_{MAX}) was summarized and evaluated clinically.

A mixed-effect model was used to evaluate bioequivalence. The model included fixed effects of treatment, sequence and period, and a random effect of subject nested within sequence. Prior to the analysis, C_{MAX} and AUC were natural logarithm transformed. Bioequivalence is established because the back-transformed estimated upper and lower bounds of the 90% confidence interval for geometric mean ratios (generic:RLNAD) of both C_{MAX} and AUC are contained within the acceptance limits of 0.80 to 1.25.

Results:

As seen in the table below, C_{MAX} and AUC fall within the prescribed bounds (Table II.1.). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.1. Bioequivalence Evaluation

Parameter	Generic Mean	RLNAD Mean	Ratio[◊]	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	22031.0[†]	21235.7[†]	1.04	0.99	1.08
C_{MAX} (ng/mL)	3380.6[†]	3311.2[†]	1.02	0.97	1.07
T_{MAX} (hours) (SD)[‡]	1.81 (0.75)[‡]	1.51 (0.62)[‡]	NE	NE	NE

[†] Geometric mean
[‡] Arithmetic mean and standard deviation (SD)
[◊] Ratio = Test/Reference
CI = confidence interval
NE = not estimated

Adverse Reactions:

There were no serious adverse events reported during the study.

Conclusions:

The *in vivo* bioequivalence study demonstrated that the generic 136 mg Enrofloxacin Flavored Tablets (enrofloxacin) and the RLNAD 136 mg Baytril® (enrofloxacin) Taste Tabs® are bioequivalent in dogs.

B. Blood-level Bioequivalence Study in Cats

Title: Pivotal Bioequivalence Study of Baytril® (Enrofloxacin) Taste Tabs® and Generic Enrofloxacin Flavored Tablets Administered Orally to Cats under Fasted Conditions. (Study No. AKR501-002)

Study Dates: February 1, 2022 to July 20, 2022

Study Locations:

In-life phase: Ontario, Canada

Bioanalytical testing: Somerset, New Jersey

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 22.7 mg Enrofloxacin Flavored Tablets (enrofloxacin) and the RLNAD 22.7 mg Baytril® (enrofloxacin) Taste Tabs® in fasted cats.

Study Animals: Thirty healthy, purpose-bred, male domestic shorthair cats between 480 days and 832 days of age on study day 0 and weighing between 4.6 kg and 6.1 kg (when measured on study day -3).

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies.

Drug Administration: Each animal received 22.7 mg of either the generic or RLNAD enrofloxacin according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The plasma concentrations of enrofloxacin were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health and adverse events.

Statistical Methods:

The laboratory study was conducted as a randomized, masked two-period, two-sequence, two-treatment, single-dose crossover design using 30 cats with a 14-day washout between periods. Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C_{MAX} and AUC. Time to maximum concentration (T_{MAX}) was summarized and evaluated clinically.

A mixed-effect model was used to evaluate bioequivalence. The model included fixed effects of treatment, sequence and period, and a random effect of subject nested within sequence. Prior to the analysis, C_{MAX} and AUC were natural logarithm transformed. Bioequivalence is established because the back-transformed estimated upper and lower bounds of the 90% confidence interval for geometric mean ratios (generic:RLNAD) of both C_{MAX} and AUC are contained within the acceptance limits of 0.80 to 1.25.

Results:

As seen in the table below, C_{MAX} and AUC fall within the prescribed bounds (Table II.2.). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.2. Bioequivalence Evaluation

Parameter	Generic Mean	RLNAD Mean	Ratio◊	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	13563.0†	12780.4†	1.06	1.03	1.09
C_{MAX} (ng/mL)	1355.1†	1290.9†	1.05	0.98	1.12
T_{MAX} (hours) (SD)‡	1.70 (1.13)‡	1.99 (1.54)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◊ Ratio = Test/Reference
CI = confidence interval
NE = not estimated

Adverse Reactions:

There were no serious adverse events reported during the study.

Conclusions:

The *in vivo* bioequivalence study demonstrated that the generic 22.7 mg Enrofloxacin Flavored Tablets (enrofloxacin) and the RLNAD 22.7 mg Baytril® (enrofloxacin) Taste Tabs® are bioequivalent in cats.

C. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 22.7 mg enrofloxacin flavored tablet strength in cats and the 136 mg enrofloxacin flavored tablet strength in dogs. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 22.7 mg and 68 mg enrofloxacin flavored tablet strengths in dogs and 68 mg and 136 mg enrofloxacin flavored tablet strengths in cats was requested. To qualify for a biowaiver for each of these product strengths, comparative *in vitro* dissolution studies were conducted to determine the dissolution profiles of the generic 22.7 mg, 68 mg, and 136 mg enrofloxacin flavored tablets.

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: 0.05M Phosphate buffer, pH 6.8
- Dissolution medium volume: 1000 mL
- Temperature: 37 °C
- Paddle speed: 75 rpm
- Number of vessels: 12
- Data points: 5, 10, 15, 20, and 30 minutes

The generic drug lot number used in the *in vivo* bioequivalence study was the same lot used to support the *in vitro* profile comparisons. Analytical method validation was required to ensure that the quantification of drug concentrations in all samples was accurate and precise.

To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%. The percent coefficient of variation for all generic product profiles was within acceptable limits. Only one measurement should be considered after 85% dissolution of one of the products. The similarity factor (f_2) should be greater than 50 to ensure sameness or equivalence of two profiles.

Study results demonstrate similar dissolution profiles for all comparisons. However, because of rapid dissolving characteristics (>85% in 15 minutes) in all strengths, a dissolution profile comparison using the f_2 test is unnecessary. When comparative profiles between tablets do not require an f_2 test because of rapid dissolution or when the f_2 value is ≥50, the product strengths used in the comparison qualify for a biowaiver. Therefore, a biowaiver for the generic 22.7 mg and 68 mg enrofloxacin flavored tablet strength in dogs and 68 mg and 136 mg enrofloxacin flavored tablets strengths in cats is granted.

III. HUMAN FOOD SAFETY

This drug is intended for use in dogs and cats. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this ANADA.

IV. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Enrofloxacin Flavored Tablets:

For use in animals only. Keep out of reach of children.

Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact with skin, wash skin with soap and water. Consult with a physician if irritation persists following ocular or dermal exposure. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

V. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the FD&C Act. The data demonstrate that Enrofloxacin Flavored Tablets, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.